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NMRI 96-05 March 1996

STATISTICALLY BASED DECOMPRESSION TABLES IX: PROBABILISTIC MODELS OF THE ROLE OF OXYGEN IN HUMAN DECOMPRESSION SICKNESS

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NOTICES

TECHNICAL REVIEW AND APPROVAL

NMRI 96-05

The experiments reported herein were conducted according to the principles set forth in the current edition of the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This technical report has been reviewed by the NMRI scientific and public affairs staff and is approved for publication. It is releasable to the National Technical Information Service where it will be available to the general public, including foreign nations.

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	March 1996	TECHNICAL 1/91 - 12/93

4. TITLE AND SUBTITLE
Statistically based decompression tables IX: Probabilistic models of the role of oxygen in human decompression sickness.

5. FUNDING NUMBERS
PE - 63713N
PR - M0099
TA - .01A
WU - 1002

6. AUTHOR(S)
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Naval Medical Research Institute
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8901 Wisconsin Avenue
Bethesda, Maryland 20889-5607

8. PERFORMING ORGANIZATION REPORT NUMBER
NMRI 96-05

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Naval Medical Research and Development Command
National Naval Medical Center
Building 1, Tower 12
8901 Wisconsin Avenue
Bethesda, Maryland 20889-5606

10. SPONSORING/MONITORING AGENCY REPORT NUMBER
DN177792

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution is unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

While probabilistic models of human decompression sickness (DCS) have been successful in describing both the level and timing of DCS risk in a wide variety of N_2-O_2 data, they have failed to account for the observed DCS risk in the currently available collection of dives with significant periods of 100% oxygen breathing. The best model to date, calibrated with over 2300 air and N_2-O_2 dives, under-predicts the DCS risk of these O_2 dives by 60%, whether O_2 is breathed during in-water decompression or during surface decompression procedures. This overestimation of the benefit of O_2 is due to an exaggerated acceleration of N_2 wash-out during O_2 breathing. Seven-hundred and twenty-nine O_2 decompression and surface decompression dives were added to the calibration data set. Fitting the existing 'base' model to the new combined data set resulted in some improvement in DCS prediction in O_2 data, but DCS predictions remained about 30% below the observed level. Three classes of O_2-specific modifications to the 'base' model were proposed: 1) modification of inert gas kinetics as a function of O_2 pressure, 2) direct contribution of DCS risk as a function of either O_2 pressure or fraction, 3) a separate O_2 risk compartment with independent O_2 wash-in and wash-out kinetics. Each of these modifications attempts to include O_2 as an explicit contributor to DCS risk, where the 'base' model considers only N_2 as risk producing. Six of the resulting seven models slightly improved the fit to the data, with only the separate O_2 compartment model resulting in a significant improvement in fit. The estimated O_2 time constant for this model is very short at 0.4±0.3 minutes. This model is a good predictor of DCS incidence in both the original N_2-O_2 and the new O_2 data. In contrast to the 'base' model, this O_2 model is able to distinguish between O_2 dives of different risk level. The success of this 'O_2 Compartment' model suggests that O_2 may contribute to DCS risk over short intervals following exposure to high levels of PO_2.

14. SUBJECT TERMS
decompression, modeling, oxygen

15. NUMBER OF PAGES
35

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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ACKNOWLEDGEMENTS

This work was supported by Naval Medical Research and Development Command Work Unit No. 63713N M0099.01A-1002. The opinions and assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the United States Navy or the naval service at large.

We gratefully acknowledge Dr. A.L. Harabin for a careful critical reading of the manuscript and Ms. S. Mannix for meticulous editorial assistance.

INTRODUCTION

Probabilistic models of human decompression sickness (DCS) have been successful in describing the occurrence, and even the time of occurrence, of DCS (5,12,16,17,19,20). The successful models thus far have not dealt explicitly with O_2, but have considered N_2 or He to be the only contributor to DCS risk. Such models have not performed well in prediction of DCS in dives that use a high fraction (40 - 100%) of oxygen in the breathing gas during decompression (12). Occurrence of DCS in these dives is systematically under-predicted by about 60%.

Previous models have been fitted to a collection of over 2300 well documented experimental Air and N_2-O_2 dives (12,18). While the majority of these dives use compressed air (21% O_2, regardless of pressure), there are also a large number of dives with enriched oxygen atmospheres, either as a constant partial pressure of oxygen (PO_2), usually 0.7 ata, or as a constant fraction (≤40%) of O_2 (F_2). For this study, 729 dives using ≈100% O_2 during in-water or surface decompression are added to the data set, for a total of 3112 dives. A wide variety of dives are represented in this expanded data set, including single, repetitive, multi-level, surface decompression and multiple day, or saturation, dives. Important time of symptom information (18,19) is included for all DCS and many marginal cases.

The emphasis of this study is a set of modifications to the previous 'base' model in an attempt to identify a specific oxygen effect in the accumulation of DCS risk. The ideal modification would improve, or leave undisturbed, the 'base' model's success with N_2-O_2 data while achieving a similar ability to describe the O_2 decompression data. Simply fitting this 'base' model to the combined data set, although an improvement, does not achieve the desired result. The oxygen effects explored here are of three forms: 1) a PO_2-dependent alteration of the inert

gas wash-in/wash-out kinetics (1), 2) a direct contribution to the N_2 tissue tension as a function of either PO_2 or FO_2 (2,3,15), and 3) a parallel, independent wash-in and wash-out of PO_2. Models similar to some of those explored here have been previously described (21), but were fitted to sub-sets of the current data, with a limited range of both FO_2 and PO_2.

DATA

The data sets used in fitting models in this report were taken from the dive data we have described in detail elsewhere (18). The dives used here are from carefully controlled and well documented experimental dives conducted in the U.S., Canada, and Great Britain. The basic data set, **A** in Table 1, used in the development of the 'base' model (12), contains 2383 dives. The data set with ≈ 100% O_2 breathed during decompression included in this analysis, **B** in Table 1, contains 729 dives, all from the Defense and Civil Institute for Environmental Medicine (DCIEM), Toronto, Ontario, Canada (7-9,11).

From the basic set of dives in data set **A** there are 131 DCS and 75 marginal cases, giving an overall DCS incidence of 5.8%. The O_2 decompression data contain 17 DCS and 4 marginal cases, for an incidence of 2.4%. Marginal cases are taken to be equal to 0.1 DCS case. For a discussion of the importance of the value assigned to marginal symptoms, see Parker et al. (12). Table 1 gives the distribution of dive types and the number of dives and DCS cases for each data category.

Data Set	Category	Dives	# DCS	Marg*	% DCS	PO_2 Range (ata)	FO_2 Range (%)
	Single - Air	876	45	9	5.2	0.21-4.0†	0.21
	Repet - Air	194	14	0	7.2	0.21-1.3	0.21
A	Single - non Air	772	29	18	4.0	0.19-1.5	0.10-0.70
	Repet - non Air	239	11	0	4.6	0.21-0.7	0.21-0.70
	Saturation - N_2-O_2	302	32	48	12.2	0.21-1.5	0.09-0.21
	Subtotal	2383	131	75	5.8		
B	O_2 Decompression	302	6	3	2.1	0.21-2.1	0.21-0.99
	O_2 Sur-D	427	11	1	2.6	0.21-2.6	0.21-0.98
	Subtotal	729	17	4	2.4		
	Total	3112	148	79	5.0		

* Marginal DCS = 0.1 DCS case[12]

† PO_2 > 1.5 ata in Single Air dives have a duration < 1 min.

Table 1. Summary of Data

While the majority of data set **A** consists of air dives, about 40% are dives that used an enriched oxygen atmosphere. About half of these dives used a constant PO_2 of 0.7 ata, either throughout the dive or with periods of air breathing (14,15). Some used a range of constant fractions of oxygen (10-40%), in order to obtain PO_2 values from 0.21 to 1.5 ata (21).

The high PO_2 values, up to 4.0 ata, in the Single Air category come from a few short (<5 min) dives from a submarine escape experiment (18) in which these pressures are never present for more than 1 min. Without these profiles, the PO_2 range for this category would be 0.21 to 1.5 ata.

The O_2 decompression dives being added here are of two types: air dives that use ≈100% O_2 during decompression and air dives followed by ≈100% O_2 during surface decompression procedures. To allow for inevitable imperfections in the delivery of O_2 to the diver, our data represent immersed and dry divers as having breathed 99.5% and 98% O_2, respectively. Among these data, the range of PO_2 is 0.21 to 2.6 ata, with the majority of the O_2 exposures at 1.9 or 2.2 ata, corresponding to 30 and 40 fsw decompression stop depths.

Time of DCS occurrence is included for all DCS cases and for most of the marginal cases. The time of symptom occurrence is represented in the data as an interval (T1-T2) over which symptoms appeared. T1 is taken to be the last known time the diver was entirely free of symptoms and T2 is the time at which definite symptoms were reported. The methods and rules of establishing the T1-T2 times for most reported dives are described in detail elsewhere (18).

MODELS

The best fitting model from our most recent N_2-O_2 modeling effort (12) will be used as the 'base' model for this study. This model allows for exponential wash-in and a mixed exponential-linear wash-out in each compartment (12,14). Risk accumulation for this model is characterized by an instantaneous risk proportional to the sum of the risks of each of its three parallel compartments;

$$r = \sum_{i=1}^{3} A_i \left(\frac{P_{tis}i - Pamb - Thr_i}{Pamb} \right) \quad ; \qquad r \geq 0 \tag{1}$$

where; A_i is a scale factor, $P_{tis}i$ is the tissue gas pressure for the ith compartment and is a function of a time constant, α_i, and a linear-exponential kinetic crossover parameter, PXO_i and includes the contribution of metabolic gases (12). $Pamb$ is the ambient pressure and Thr_i is the risk threshold parameter (5,17) for the ith compartment. Tissue pressure must exceed ambient plus the threshold in order for that compartment to generate a non-zero instantaneous risk and no compartment may make a negative contribution to risk.

This 'base' model, when fitted to the original N_2-O_2 data set, has been shown to be successful in predicting the DCS incidence in those data (12). However, the 'base' model's prediction of DCS incidence in the O_2 decompression data is consistently and substantially low. Table 2 lists the observed DCS cases for each of the data categories, along with the number of cases predicted by the 'base' model. The first column of predicted DCS is for the 'base' model fitted to the original N_2-O_2 data set (**A**). This data/model combination results in a 60% under-prediction of DCS for the O_2 data. Note that the under-prediction of DCS occurrence is essentially equal in both O_2 Decompression and O_2 Surface-Decompression (Sur-D) data. The second column of predicted DCS is the result of adding the O_2 dives to the fitting data set (**A+B**). This new fit raises the 'base' model's prediction of DCS for the O_2 data considerably, so that it is now a 30% under-prediction. However, the observed DCS incidence for the O_2 dive data remain outside the propagated 95% confidence limits of the predictions (6), making this data/model

combination a statistical "failure". It is interesting to note that while the 'base' model fitted to **A+B** moderately over-predicts DCS risk overall in data set **A**, it does a slightly better job of predicting DCS risk in three of the five categories of data set **A** than when fitted to **A** alone.

	Data Set	DCS Cases Observed	DCS Cases Predicted by Base Model: Fitted to A	Fitted to A+B
	Single Air	45.9	40±7	42±7
	Repetitive Air	14.0	13±3	14±3
	Single non-Air	30.8	31±6	35±6
A	**Repetitive non-Air**	11.0	15±3	16±3
	Saturation	36.8	40±12	36±9
	Total	138.5	139±23	144±22
	O_2 Decompression	6.3	2±1	4±1
B	**O_2 Surface Decom.**	11.1	4±3	9±2
	Total	17.4	6±4	13±4

Table 2. Base Model prediction of DCS incidence (±95% confidence limits).

For two of the model's three compartments, the estimated parameter values (time constants, thresholds, etc.) for the 'base' model's fits to data set **A** and to **A+B** are the same, within their estimated confidence limits. The exceptions, with substantial changes in estimated values, are the time constant, α_3, and the threshold, Thr_3, both from the third compartment. This time constant (407±22 min), estimated by the fit to **A+B**, is 16% shorter than that fitted to **A** alone

(488±41 min), and the threshold is 75% smaller (0.44±0.3 versus 1.75±0.7 fsw). Although the shorter time constant will result in faster inert gas wash-out, it will mean faster gas uptake as well, potentially resulting in higher overpressures, depending on the specifics of the dive. For example, for saturation dives, the shorter time constant results in a lower prediction of DCS occurrence because only wash-out is affected; in saturation dives this compartment's gas uptake is saturated for either time constant.

The more important difference, for a majority of the dive data, is the lower absolute supersaturation threshold, which allows a greater risk accumulation for almost all dives. It is this lower estimated threshold that accounts for much of the increased DCS incidence predicted for both **A** and **B** by the fit to **A+B** shown in Table 2.

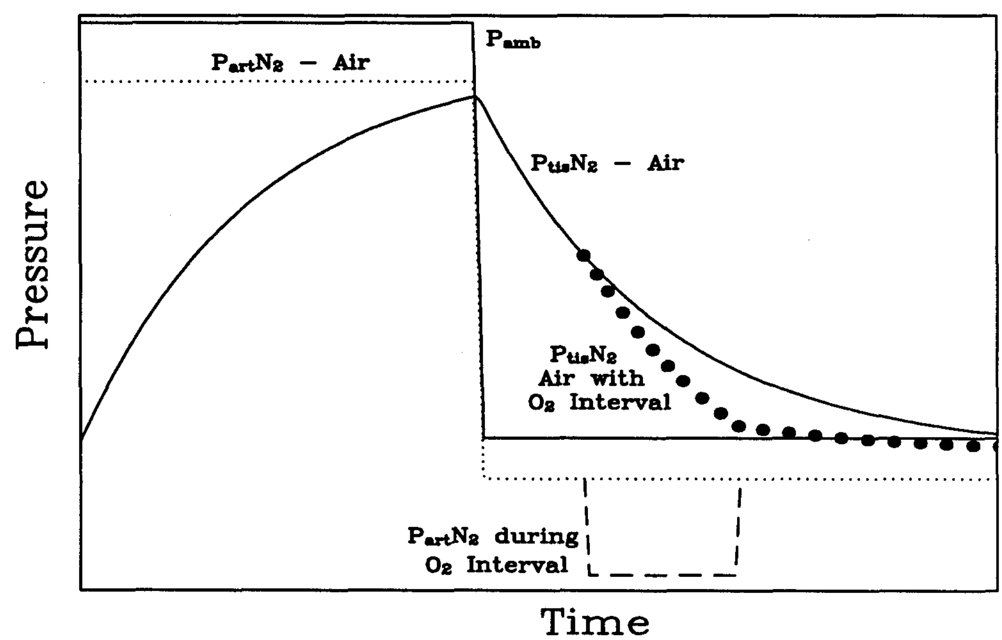

Figure 1. Accelerated N_2 washout during O_2 breathing.

Figure 1 illustrates the underlying reason for the 'base' model's under-prediction of DCS risk in the O_2 decompression data. In the hypothetical dive profile shown, two possible washout curves are plotted: one for a diver who breathes Air (solid curve) during the decompression stop, another for a diver who breathes 100% O_2 (dotted curve) during a portion of the stop. The duration of the O_2 period is indicated by the drop in arterial N_2 ($P_{art}N_2$) level below that for breathing Air. During the O_2 breathing period tissue N_2 wash-out accelerates because the asymptote for the model's calculated N_2 tissue pressure, $P_{art}N_2$, is then essentially zero. Since the model considers DCS risk to be proportional to the area between the N_2 tissue pressure curve and ambient pressure, risk is reduced, both in magnitude and duration, due to the O_2 breathing period.

While this reduction in risk is in qualitative agreement with the idea that breathing O_2 during decompression reduces the risk of DCS, the effect is exaggerated in the 'base' model when compared to the observed DCS incidence in the available O_2 decompression data. We need to modify the 'base' model either to reduce the N_2 wash-out rate during O_2 breathing periods, or to introduce a specific O_2-based risk contribution.

Three types of modifications to the 'base' model are proposed in this study, each with the aim of better describing the DCS risk observed in the O_2 decompression data while maintaining the model's ability to describe the N_2-O_2 data set as a whole. These modifications to the 'base' model attempt to involve either the partial pressure or the fraction of oxygen present during the dive in the accumulation of DCS risk. We seek to accomplish this through **a)** modification of inert gas wash-in/wash-out kinetics, **b)** direct PO_2 or FO_2 contribution to risk, or **c)** a PO_2 based kinetic risk compartment.

Kinetic Modifications

The first class of modifications (Models 1 & 2) attempts to include the effect of breathing high pressures of O_2 by altering the inert gas kinetic time constants for each compartment as a function of PO_2. This class of modifications is based on experimental results in which a reduction of whole body N_2 washout is observed with exposure to increasing PO_2 (1). This reduced N_2 wash-out is attributed to simultaneously observed reductions in cardiovascular parameters, including heart rate, perfusion, and blood flow, the combined effects of which we can model as slower kinetic time constants.

In Model 1, the modified time constant for each compartment is defined as

$$\alpha_i = \alpha_{0_i} \cdot \left(1 + \left(k_1 \cdot PO_2\right)^{k_2}\right) \tag{2}$$

where α_{0i} is the unmodified inert gas time constant for the ith compartment, to be estimated by fitting to data, PO_2 is the oxygen pressure during the time of interest, and k_1 and k_2 are parameters to be estimated from the data. Model 1 adds up to two parameters per compartment to the 'base' model.

In Model 2, the modified compartment time constant is defined as

$$\alpha_i = \alpha_{0_i} \cdot \left(\left(\frac{PO_2}{P_{surf}O_2}\right)^{k1}\right) \tag{3}$$

with the terms defined as for Model 1, above. The term $P_{surf}O_2$ is the PO_2 of blood at 1 ata of air. Model 2 adds only one parameter to be estimated per compartment.

Figure 2 shows a range of effects that Models 1 and 2 might have on an N_2 kinetic time constant, for several values of k_1 and k_2, over the PO_2 range contained in the data. The value on the y-axis in these plots is the exchange retardation factor within parentheses in equations (2) and (3).

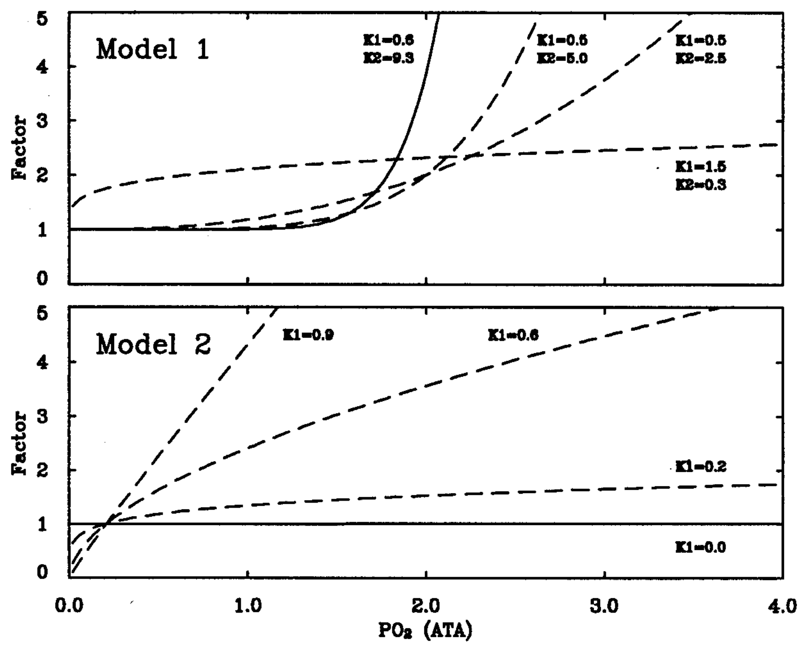

Figure 2. Range of responses for Models 1 and 2

It is clear that a wide range of kinetic modifications are possible with these functions, producing from subtle to pronounced effects, depending on the values of the parameters k_1 and k_2. In particular, Model 1 is capable of producing a seemingly desirable modification that has virtually no effect on α_0 for values of PO_2 generally observed in the air dives (PO_2 usually below 2.0 ata), and an increasing effect on α_0 for higher PO_2 levels.

Direct Risk Contribution

The second class of modifications (Models 3 - 6) proposes a direct addition to the instantaneous risk, as a function of either the PO_2 or FO_2 level in the breathing gas. These modifications are based on the idea that at certain high levels of O_2 exposure, some of the O_2 present acts essentially as an inert gas and may therefore contribute to DCS risk (2-4,13,15,21).

For Models 3 through 6, an "O_2 effect" is added to the instantaneous risk function, Equation (1), to make;

$$r = \sum_{i=1}^{3} A_i \left(\frac{P_{tis}i - Pamb - Thr_i + EFO_{2i}}{Pamb} \right) \; ; \qquad r \geq 0 \tag{4}$$

As for Equation (1), the term inside the summation must be greater than zero, i.e., no compartment may make a negative risk contribution.

Pressure-based Direct Contribution

In Model 3, the O_2 contribution to instantaneous risk is a function of the pressure of oxygen present beyond that in air on the surface. We restrict the risk contribution to PO_2 values greater than $P_{surf}O_2$ so that no DCS risk accumulates while breathing air on the surface.

$$EFO_{2_i} = \left(k_1 \cdot (PO_2 - P_{surf}O_2)\right)^{k_2} \tag{5}$$

In Model 4, only the pressure of oxygen present beyond a PO_2 threshold, O_2thr, contributes to DCS risk. The value of O_2thr was set at 1.5 ata for this study, based on the range of PO_2 in the current data set. As seen in Table 1, 1.5 ata is the upper limit of PO_2 in the non-O_2

data sets (with the exception of a few deep submarine escape exposures of short duration in the Single Air category).

$$EFO_{2_i} = \left(k_1 \cdot \left(PO_2 - O_2thr\right)\right)^{k_2} \tag{6}$$

Figure 3 shows a range of possible functionalities by which Models 3 and 4 can contribute to the DCS risk. Note that, depending on the values of $k1$ and $k2$, either model can vary its response greatly, from a gentle increase in EFO_2 as PO_2 increases to a sudden increase over a small PO_2 interval. Also note the restricted range of PO_2 in which Model 4 can contribute risk due to the selected value of its O_2thr parameter.

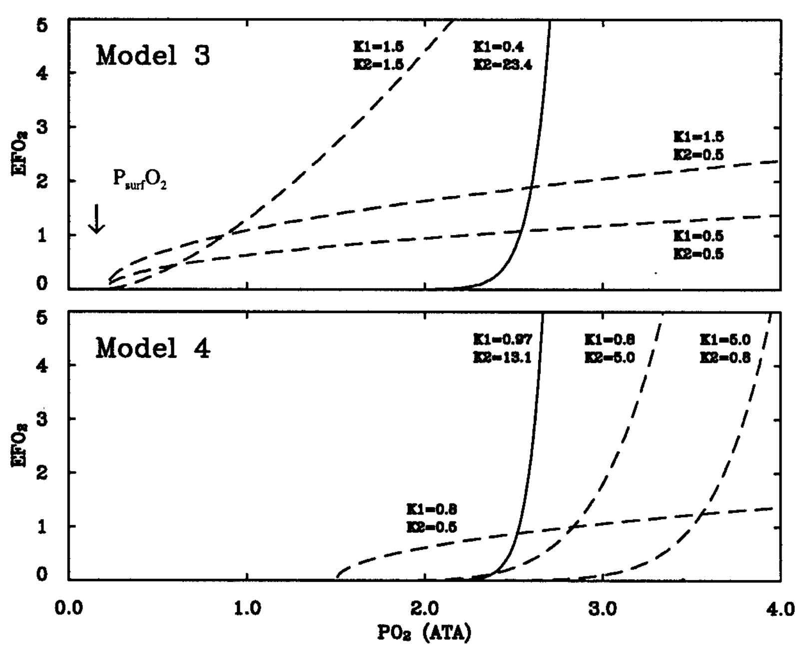

Figure 3. Range of responses for Models 3 and 4

Fraction-based Direct Contribution

In Table 1 we made a distinction between the O_2 decompression dives and the remaining data on the basis of PO_2, although there is some overlap in PO_2 between the two types. This indefinite boundary allows any PO_2-based risk contribution to be implemented not only for the O_2 data sets, where it is needed, but also for some parts of the remaining data, where it may not be needed. A clearer distinction can be made between these data sets on the basis of the fraction of O_2. Although the dives in data set **B** use air at depth, their subsequent exposure to 100% oxygen makes these dives clearly different from the others. Since it is during these O_2 exposures that the 'base' model fails to accumulate sufficient risk, we can attempt to make an O_2-based risk contribution only during these high FO_2 exposures.

Model 5 is based on the fraction of O_2 present and uses the parameter k_2 as a threshold of O_2 fraction below which no contribution is made to risk.

$$EFO_{2_i} = \left(k_1 \cdot (FO_2 - k_2)\right) \tag{7}$$

Model 6 is similar to Model 3, but uses the fraction, rather than the pressure, of O_2 present in excess of the fraction of O_2 present on the surface (breathing air), in determining its risk contribution.

$$EFO_{2_i} = \left(k_1 \cdot (FO_2 - F_{surf}O_2)\right)^{k_2} \tag{8}$$

Figure 4 shows a range of possible contributions that Models 5 and 6 can make to DCS risk for the range of FO_2 values found in the current data.

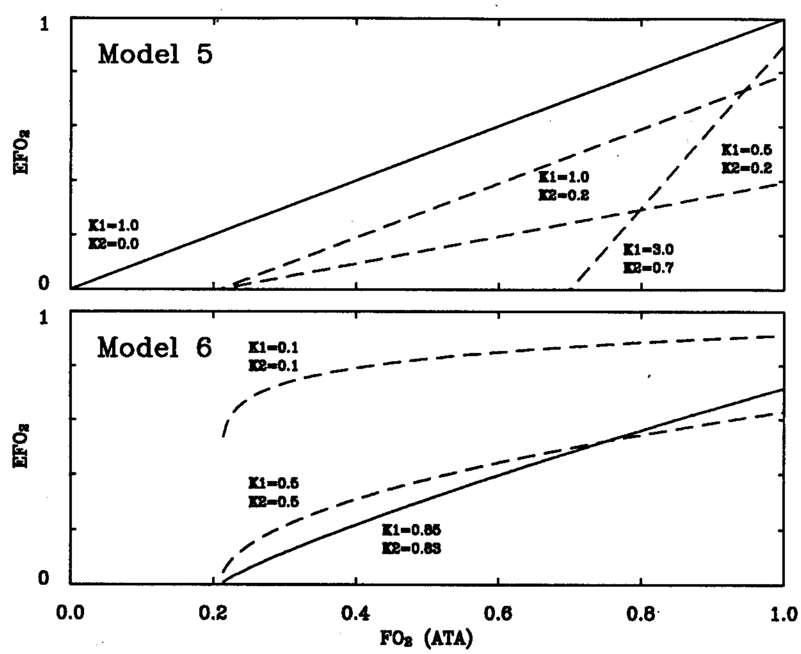

Figure 4. Range of responses for Models 5 and 6

Each of the modifications in this direct risk contribution class (Models 3 - 6) increases the number of parameters per compartment to be estimated from the data by two; k_1 and k_2. The effect of the modifications of Models 1 - 6 can each be nullified simply by setting the parameter k_1 to 0, simplifying in every case to the 'base' model.

O_2 Kinetic Compartment

The third class of modification (Model 7) adds a fourth parallel risk compartment in which $Ptis_4$ is based on PO_2 rather than PN_2 and uses only single exponential kinetics for gas wash-in and wash-out. This model should have the ability to isolate the risk contribution due to high pressures of oxygen in this fourth compartment, while leaving the N_2-based risk accumulation relatively undisturbed in the three original compartments of Equation 1.

$$r_4 = A_4\left(\frac{P_{tis}O_2 - Pamb - Thr_4}{Pamb}\right) \quad ; \quad r_4 \geq 0 \tag{9}$$

In order to get an overpressure, and therefore a risk contribution from this compartment, the 'tissue pressure' of oxygen, $P_{tis}O_2$, must exceed ambient pressure. For Air dives, it is not possible to obtain this much overpressure with bottom depths shallower than about 5 ata (about 132 fsw). Risk on deeper air dives would require rapid decompression either to a shallow stop or the surface so that sufficient overpressure was established before the 'tissue pressure' kinetics of O_2 washout $P_{tis}O_2$ below ambient pressure. The constant PO_2 dives prevalent in the non-Air portion of data set **A** will never invoke an overpressure in this compartment because they maintain a fixed PO_2 of 0.7 ata. The primary source of potential overpressures in this fourth compartment are the periods of 100% O_2 breathing in data set **B**.

PARAMETER ESTIMATION

The parameters for each model are estimated from the data using a modified Marquardt (11) nonlinear estimation routine. The probability of each outcome, needed for the estimation, comes from the following:

if DCS ***is not*** observed;

$$P(no\,DCS) = e^{-\int_0^{+24hrs} r\,dt} \tag{8}$$

if DCS ***is*** observed in the interval T1 - T2:

$$P(DCS) = \left(e^{-\int_0^{T1} r\,dt}\right) \cdot \left(1 - e^{-\int_{T1}^{T2} r\,dt}\right) \tag{9}$$

The calculation of P(DCS) combines the probability of not observing DCS over the interval from 0 to T1 with the probability of observing DCS over the interval T1 to T2. Any risk remaining after T2 in this case is ignored, where in the case of no DCS, all risk out to 24 h (48 h for saturation dives) after surfacing is included.

Since each of the proposed models is a modification of, and can be simplified to, the 'base' model, a likelihood ratio test (5,6) can be used to test for the significance of the added parameters contained in each modification. A proposed model will have a significantly improved fit to the data compared to the 'base' model, if its LL increases by more than 2 for 1 added parameter, or by 3 for 2 added parameters.

Each model, including the 'base' model, is fitted to the combined data set (**A+B**). Models 1 through 6 allow for up to 6 new parameters (2 per kinetic compartment) to be estimated, in addition to the 'base' model's kinetic time constants, scale factors, thresholds, and linear-exponential crossover parameters. Some or all of the added parameters may not add significantly to the improvement of the fit, as judged by the likelihood ratio test. In order to arrive at the form for each model that would maximize the improvement in LL with the fewest added parameters, each model was fitted to the data with incremental addition of estimated parameters.

Each of Models 1 through 6 allows for all three kinetic compartments to use the same fitted k_1 and k_2 values, or for each compartment to have independently fitted k_1 and k_2 values. Using Model 1 as a typical example, the fewest possible additional fitted parameters is two: one k_1 and one k_2 parameter applied to all three compartments. Application of the modification to only one compartment, setting $k_1 = 0$ for the other two compartments, also results in two added estimated parameters. If the modification is applied to two or three compartments independently, there will be 4 or 6 added estimated parameters, respectively. Model 2 contains only a k_1 parameter, so it will add 1, 2, or 3 estimated parameters, as above.

The added parameters of Model 7 pertain only to a fourth kinetic compartment, and will add at least two estimated parameters, a time constant and scale factor. A threshold may be included for this compartment if found to be significant.

RESULTS OF FITTING

After fitting each model to the data set by incrementally adding estimated parameters by the above procedure, the best fit of each model was found to add no more than two estimated parameters to the 'base' model, which contains eight estimated parameters (12). Model 1 and Models 3 through 6 each add two estimated parameters, k_1 and k_2, but only for the third compartment; the k_1 and k_2 parameters for the first and second compartments proved not to significantly improve the fit. This O_2 effect emphasis on the third (longest time constant) compartment is not surprising, since the long-lasting overpressure that this compartment can provide will be useful in adding the necessary risk accumulation. No improvement of fit was found for any value of k_1 in Model 2.

Table 3 lists the LL values and the number of additional estimated parameters found for the best fit of each model to data set **A+B**. Only Model 7 produced a significant improvement in the fit to the data, with a likelihood improvement of 4.2 for 2 added parameters.

	Models							
	Base	**(1)**	**(2)**	**(3)**	**(4)**	**(5)**	**(6)**	**(7)**
LL	-813.3	-810.8	-813.3	-811.7	-811.4	-810.8	-811.3	-809.1
# of Added Parameters	-	2	0	2	2	2	2	2

Table 3. Log Likelihood Results for Fitting to Data Set A+B

Table 4 lists the best fit parameters and standard errors estimated for each model by fitting to data set **A+B**. The estimated parameter values for all seven models are listed here, regardless of whether a model achieved a significant improvement of fit to the data compared to the 'base' model. We show "less than significant" parameter estimates since they may still suggest something about the nature of an O_2 effect in the data.

Parameters in the upper section of Table 4 are those found to be significant in fitting the 'base' model: For example, only PXO_2 is listed since the PXO parameters for compartments 1 and 3 did not significantly improve the fit. Those parameters in the lower section of the table are the added O_2 effect parameters as they apply to Models 1 - 7. The k_1 and k_2 values listed for Model 1 and Models 3 through 6 apply only to compartment 3, since these parameters did not improve the fit when applied to Compartments 1 and 2.

	Models							
	Base	**(1)**	**(2)**	**(3)**	**(4)**	**(5)**	**(6)**	**(7)**
α_1	1.07 (0.50)	1.09 (0.52)	1.07 (0.50)	3.82 (3.50)	3.99 (3.82)	0.97 (0.49)	0.98 (0.51)	1.14 (0.57)
α_2	26.6 (11.4)	44.4 (18.6)	26.6 (14.4)	27.2 (10.9)	27.3 (11.0)	25.2 (11.0)	25.3 (11.1)	26.8 (10.3)
α_3	404.5 (21.3)	443.1 (37.4)	404.5 (21.3)	405.2 (21.3)	405.3 (21.2)	404.9 (22.0)	403.2 (23.7)	411.6 (22.4)
A_1	6.1E-3 (5.1E-3)	5.9E-3 (5.0E-3)	6.1E-3 (5.1E-3)	8.6E-4 (9.7E-4)	8.1E-4 (9.3E-4)	7.0E-3 (6.4E-3)	6.8E-3 (6.2E-3)	5.4E-3 (4.8E-3)
A_2	5.1E-5 (2.3E-5)	9.1E-5 (4.0E-5)	5.1E-5 (2.3E-5)	4.9E-5 (1.5E-5)	4.9E-5 (1.5E-5)	4.5E-5 (1.5E-5)	4.5E-5 (1.5E-5)	5.0E-5 (1.5E-5)
A_3	1.0E-3 (1.5E-4)	9.9E-4 (1.7E-4)	1.0E-3 (1.5E-4)	1.0E-3 (1.5E-4)	1.0E-3 (1.5E-4)	1.0E-3 (1.5E-4)	1.0E-3 (1.5E-4)	9.7E-4 (1.5E-4)
PXO_2	0.0 (Fixed)	1.00 (0.94)	0.0 (F)	0.0 (F)	0.0 (F)	0.0 (F)	0.0 (F)	0.0 (F)
Thr_3	0.44 (0.30)	1.04 (0.59)	0.44 (0.30)	0.43 (0.30)	0.43 (0.30)	6.39 (2.81)	0.41 (0.31)	0.41 (0.31)
$k_1^\dagger$		0.56 (0.09)		0.43 (0.07)	0.97 (0.29)	0.97 (0.46)	0.85 (0.91)	
$k_2^\dagger$		9.30 (8.30)		23.4 (8.8)	13.1 (5.4)	0.0 (F)	0.83 (0.57)	
α_4								0.40 (0.30)
A_4								0.12 (0.35)

Table 4. Estimated Parameters (and SE) for Models fitted to Data Set A+B

† k parameter applied to third compartment only.

Several parameter values are shown with a value of 0.0 and a standard error of (F). In these cases, the estimated value of the parameter is very close to zero and has a large standard error, giving a confidence limit range which includes zero. This results from the estimation

routine's handling of very small optimal parameter values. We fix these parameters to 0.0, with no degradation in fit. This commonly occurs in the case of PXO_2, for which a value of 0.0 indicates that linear kinetics are present for any inert gas supersaturation in the second compartment.

Ideally, the O_2 effect parameters of any model would describe the added O_2 data, **B**, and allow the basic parameters to better describe the data in **A**. The estimated parameters for Model 1 suggest that it has had some success toward this end. Each of the basic parameters estimated for Model 1 is within the standard error of that parameter's value in the 'base' model fit. However, parameter values for Model 1 are very similar to those estimated by the 'base' model when fitted only to the original data set, **A** (12), suggesting that the influence of the added data, **B**, is at least partly being accounted for by the added k_1 and k_2 parameters. The estimated k_1 and k_2 values indicate one type of O_2 effect which seems to fit the combined data set; little alteration of the N_2 based kinetics for values of PO_2 below 1.5 ata, but a rapidly increasing effect for higher values of PO_2, up to an exchange retardation factor of almost 50 at 2.6 ata. The curve for these estimated parameter values is shown as the solid line in the upper plot of Figure 2.

The estimated parameters for Model 2 are the same as those for the 'base' model. The estimated k_1 parameter value is 0, so that the base time constant is multiplied by 1.0 (Eqn. 3) and no O_2 effect is present. The lack of an exchange retardation effect for Model 2 is shown as the flat line at Factor = 1.0, in the lower plot of Figure 2.

Models 3 and 4 share nearly identical estimated basic parameters. Their estimated k_1 and k_2 values result in very similar O_2 effect curves, shown as solid lines in Figure 3. While the 'added-risk' type of O_2 effect in these models is quite different from the time constant alteration

of Model 1, the nature of the PO_2 dependence is essentially the same: no effect for low values of PO_2, then an abrupt increase in effect over a short interval of higher PO_2. In Model 1, this O_2 effect jump takes place at the upper boundary of PO_2 seen in the non-O_2 data, so that there is little or no effect for Air and other N_2-O_2 data and a large effect for the O_2 decompression data. In Models 3 and 4 the jump takes place near the upper boundary of PO_2 seen in the O_2 data, so that there is little effect for any but the most extreme PO_2 exposures.

With the exception of their risk thresholds, Models 5 and 6 also have nearly identical basic parameters. There is a strong correlation between the Thr_3 and k_2 parameters in Model 5, so that any change in one is directly reflected in the other. Since a smaller value of k_2 results in a larger O_2 effect risk contribution for any given FO_2, the threshold correspondingly increases to reduce risk accumulation. In the range of about 1 to 7 fsw, the specific value of Thr_3 has little effect on the fit to these data, as long as the k_2 value is allowed to adjust in the corresponding range of about 0.2 to 0.0 (FO_2). For values of k_2 above 0.2 the strong correlation with Thr_3 vanishes, suggesting that the correlation results primarily from the Air data, which requires the higher threshold to eliminate the added and, for Air dives unneeded, O_2 effect risk. However, the overall fit of Model 5 is substantially poorer at values of k_2 above 0.2.

The estimated O_2 effect curves for Models 5 and 6, shown as solid lines in Figure 4, have a relatively gentle linear increase of effect over the FO_2 range, not the sudden jump in effect seen in Models 1, 3, and 4 for PO_2 dependency.

The estimated N_2 kinetic parameters for Model 7 are essentially unchanged from those of the 'base' model. The time constant estimated for the PO_2 risk compartment is short at 0.4 min, while its scale factor is over 20 times larger than the largest N_2 compartment scale factor.

This leads to O_2-based overpressures of short duration, but which are capable of substantial risk contributions.

The standard errors are large (75 and 300%) on Model 7's O_2 compartment parameter estimates because of the limited contribution this compartment makes to the overall DCS risk: barely 3% of the total risk accumulation for the whole data set. The fact that the confidence limits for this compartment's scale factor (A_4) include zero suggests that eliminating the O_2 compartment would not alter the fit. However, fixing A_4 to zero results in exactly the 'base' model fit, which is more than 4 LL units worse. Thus, even though the contribution this compartment makes is small, it allows Model 7 to better fit the data than the other models, as reflected in both the LL improvement as well as the DCS risk predictions described below.

PREDICTION OF DCS

Table 5 lists the DCS occurrence estimated by each of the models for the data used in fitting, divided into data sets **A** (N_2-O_2), and **B** (O_2 decompression) as listed in Table 1.

		OBS DCS	Models							
			Base	**(1)**	**(2)**	**(3)**	**(4)**	**(5)**	**(6)**	**(7)**
A	Total	**138.5**	144±22	140±22	143±22	144±22	142±22	142±22	143±22	140±22
B	Decom	**6.3**	4±1	4±2	4±1	4±1	4±1	5±2	5±2	6±2
	Surd-D	**11.1**	9±2	12±5	9±2	9±3	9±3	9±3	9±3	11±4
	Total	**17.4**	13±4	16±6	13±4	13±4	13±4	14±4	14±4	17±6

Table 5. Prediction of DCS Occurrence for all Models (fit to A+B)

From the results listed in Table 5, it is clear that only Models 1 and 7 have the specific behavior we are looking for; prediction of DCS occurrence in data set **A** centered more nearly on the observed value *and* prediction of DCS occurrence in data set **B**, which includes the observed value within its confidence limits, preferably centered on the observed value.

For data set **B** as a whole, Model 1 has the type of result desired, but since its improvement of the fit to the data was not significant as measured by LL, it cannot be considered a total success. Additionally, its predicted DCS incidence for the O_2 Decompression subset of data set **B** is unchanged from that of the 'base' model and falls short of the observed value.

Since this model was intended to incorporate the experimental observations of Anderson et al. (1), we might learn something about our models and data by comparing the behavior of Model 1 with those observations. They report 9% and 17% reductions in the volume of N_2 elimination, compared to normoxic levels, over 2 hours at PO_2 levels of 2.0 and 2.5 ata, respectively. Model 1 (Eqn. 2; using the best fit parameters shown in Table 4) yields kinetic retardation factors of 2.02 and 11.11 at PO_2 of levels of 2.0 and 2.5 ata, respectively. This retardation applies only to the slowest of the three compartments, giving N_2 wash-out time constants of 895 or 4923 min for these two PO_2 levels. Over a two-hour wash-out period these retarded time constants would result in 12.8% and 21.8% reductions in N_2 elimination compared to the unmodified time constant of 443 min. Since we make no distinction of the inert gas volume represented by each compartment, it is impossible to make a direct comparison between the reported (1) and this calculated decrease in N_2 volume elimination. However, we find a reasonable match with the reported values if we assume that the third compartment of Model 1 represents about 70% of the total inert gas volume: the calculated reductions in N_2 wash-out

would give whole body reductions of 9% and 15% for PO_2 levels of 2.0 and 2.5 ata, respectively. We will retain Model 1 as a promising candidate for fitting to larger data sets as they become available.

Models 3 and 4 show no improvement in predictive ability over the 'base' model. While Models 5 and 6 contain the observed value within the confidence limits of their DCS prediction for **B**, they retain some of the 'base' model's overprediction of occurrence in data set **A**. This modest overprediction, together with the failure of either of these models to achieve a significant improvement in the fit to the data, makes them less than successful.

Model 7 exhibits a prediction of DCS in data set **A** nearly identical to that of the 'base' model when fitted only to **A** (see Table 2). In addition, Model 7 is a good predictor of DCS occurrence in the O_2 decompression data, **B**. This, combined with the fact that it significantly improves the fit to **A+B** over the 'base' model, makes Model 7 a success by these three important measures. Note that, in contrast to Model 1, Model 7 achieves its good prediction of the overall level of DCS incidence in data set **B** by correctly predicting the incidence level in both subsets of **B**.

Table 6 shows another measure of the improvement that Model 7 provides in our ability to describe, with a single model, DCS incidence in both the original N_2-O_2 data set as well as the O_2 decompression data. In this test a model is used to group the dives in a data set by its estimation of each dive's risk level, and the observed and predicted DCS incidence for each group is compared. For example, in the first group of three columns of the lowest risk category row, 0 to 2.5%, the 'base' model fit to **A** is used to select those dives that it predicts to belong in this risk group. This set of dives is observed to have an average DCS incidence of 2.6%, while the

model predicts 1.8%; this group of dives is somewhat riskier than this model predicts. However, it can be seen that there is generally good agreement, with each higher risk level group corresponding to a higher observed and predicted incidence.

The model which we have set out to improve upon, the 'base' model fitted to data set **A**, is generally able to distinguish between dives of different risk level within data set **A**, but fails in this regard when applied to data set **B**, as shown on the right side of Table 6. Our best candidate to accomplish the desired improvement, Model 7 fitted to the combined **A+B** data set, retains much of the 'base' model's ability to distinguish the risk level of dives in data set **A**, and is also able to do so for the dives of data set **B**.

The unmodified 'base' model, when fitted to the combined **A+B** data set, gives a result intermediate between those shown in Table 6; some degradation of the prediction of DCS incidence in data set **A** and only moderate improvement in DCS prediction for data set **B**.

	Data Set A						Data Set B					
	'Base' Model (fit to A)			Model (7) (fit to A+B)			'Base' Model (fit to A)			Model (7) (fit to A+B)		
Risk Level	n	Obs	Pred	n	Obs	Pred	n	Obs	Pred	n	Obs	Pred
0.0-2.5%	535	2.6%	1.8%	630	2.7%	1.6%	708	2.5%	0.9%	550	1.9%	1.7%
2.5-5.0	614	3.6	3.7	474	3.1	4.0	21	0.0	2.9	179	4.0	3.2
5.0-7.5	643	4.3	6.2	652	4.4	6.2						
7.5-10.	298	10.6	8.5	363	10.8	8.5						
10.-100.	293	14.8	14.1	264	14.8	12.7						

Table 6. Prediction of DCS by risk level.

SUMMARY AND CONCLUSIONS

The 'base' model, while quite successful in describing DCS occurrence in a wide range of N_2-O_2 data, both within the fitted dives and for other dives, fails to accurately describe DCS occurrence in a data set of O_2 decompression dives. The substantial underprediction of DCS incidence in these dives, due to accelerated N_2 wash-out during O_2 breathing, is only modestly improved by fitting the 'base' model to the combined data set. The remaining discrepancy between observed and predicted incidence requires that O_2 itself contribute to the DCS risk. The degree of suggested effect, however, is much greater than that measured in human whole-body wash-out experiments (1) and is near the limit of possible conclusions from a human dive trial specifically designed to elicit the role of O_2 in DCS (21).

Alteration of the inert gas kinetic time constants based on PO_2, as tested in Model 1, shows some promising qualities, but is not statistically successful with the current available data set. Further explorations with this type of modification to the 'base' model may be profitable when more O_2 data become available.

Direct contribution to DCS risk, based on either PO_2 or FO_2 present, results in little or no improvement for the current combined data set.

Addition of a separate, parallel risk compartment based on PO_2, rather than PN_2, overpressure (Model 7) is the only modification of the 'base' model explored in this study that results in a significant improvement in the fit to the combined data set. The time constant estimated for this single exponential kinetic compartment is very short at 0.4 min. This brief duration of risk accumulation is offset by an unusually large estimated scale factor, which causes the O_2 supersaturation to make a large risk contribution. This model results in a nearly exact

prediction of DCS occurrence in the O_2 dives, whether looked at as a whole, separated by type of decompression (Table 5), or ranked by risk level (Table 6).

The failure of the 'base' model to describe DCS risk in a large set of O_2 decompression dives lead us to explore the idea that O_2 itself contributes to DCS risk when present in high pressures or fractions. The success of Model 7 in increasing the risk accumulated during these O_2 dives while retaining, or improving upon, the desirable behavior of the 'base' model on all other dives, suggests that O_2 can be considered to independently contribute to DCS risk over short durations following exposure to high PO_2.

REFERENCES

1. Anderson, D., Nagasawa, G., Norfleet, W., Olszowka, and A., Lundgren, C., " O_2 pressures between 0.12 and 2.5 atm abs, circulatory function, and N_2 elimination." Undersea Biomedical Research, Vol. 18, No. 4, pp. 279-292, 1991.

2. Donald, K.W., "Oxygen Bends." Journal of Applied Physiology, Vol. 7, pp. 639-644, 1955.

3. Eaton, W.J. and Hempleman, H.V., The Role of Oxygen in the Aetiology of Acute Decompression Sickness. Report 12-73, Royal Navy, Alverstoke, UK, 1973.

4. Forest, T.W. and Ward, C.A., "Effect of dissolved gas on the homogeneous nucleation pressure of a liquid. Journal of Chemistry and Physics, Vol. 66, pp. 2322-2330, 1977.

5. Hays, J.R., Hart, B.L., Weathersby, P.K., Survanshi, S.S., Homer, L.D., and Flynn, E.T., Statistically Based decompression tables IV. Extension to air and N_2O_2 saturation diving. NMRI Technical Report No. 86-51, Naval Medical Research Institute, Bethesda, Maryland, 1986.

6. Kendall, M.G., and Stewart, A., The Advanced Theory of Statistics. 4th ed. Vol. 2. London: Haffner, p. 38-180, 1979.

7. Lauckner, G.R., Nishi, R.Y., and Eatock, B.C., Evaluation of the DCIEM 1983 decompression model for compressed air diving(Series A-F). DCIEM Report 84-R-72, Defence and Civil Institute of Environmental Medicine, Toronto, Canada, Oct 1984.

8. Lauckner, G.R., Nishi, R.Y., and Eatock, B.C., Evaluation of the DCIEM 1983 decompression model for compressed air diving (Series G-K). DCIEM Report 84-R-73, Defence and Civil Institute of Environmental Medicine, Toronto, Canada, Nov 1984.

9. Lauckner, G.R., Nishi, R.Y., and Eatock, B.C., Evaluation of the DCIEM 1983 decompression model for compressed air diving (Series L-Q). DCIEM Report 85-R-18, Defence and Civil Institute of Environmental Medicine, Apr 1985.

10. Marquardt, D.W., "An algorithm for least-squares estimation of non-linear parameters." Journal of the Society of Industrial and Applied Mathematic, Vol. 11, pp. 431-441, 1963.

11. Nishi, R.Y., Lauckner, G.R., Eatock, B.C., Hewitt, J.T., Oxygen decompression techniques for compressed air diving using the XDC-2 decompression computer programmed with the Kidd-Stubbs 1971 model. DCIEM Report 84-R-19, Defence and Civil Institute of Environmental Medicine, June 1984.

12. Parker, E.C., Survanshi, S.S., Weathersby, P.K., and Thalmann, E.D., Statistically based decompression tables VIII: Linear-exponential kinetics. NMRI Technical Report No. 92-73, Naval Medical Research Institute, Bethesda, Maryland, 1992.

13. Rashbass, C. and Eaton, W.J., The Effect of Oxygen Concentration on the Occurrence of Decompression Sickness. Report 10-57, Royal Navy, Alverstoke, UK, 1957.

14. Thalmann, E.D., Phase II testing of decompression algorithms for use in the U.S. Navy underwater decompression computer. NEDU Technical Report, No. 1-84, Navy Experimental Diving Unit, Panama City, Fla., 1984.

15. Thalmann, E.D., Air-N_2O_2 Decompression Computer Algorithm Development. NEDU Technical Report, No. 8-85, Navy Experimental Diving Unit, Panama City, Fla., 1985.

16. Tikuisis, P., Weathersby, P.K., and Nishi, R.Y., "Maximum Likelihood Analysis of Air and HeO_2 Dives." Aviation, Space, and Environmental Medicine, Vol. 62, pp. 425-31, 1991.

17. Weathersby, P.K., Survanshi, S.S., Homer, L.D., Hart, B.L., Nishi, R.Y., Flynn, E.T., and Bradley, M.E., Statistically Based decompression tables I. Analysis of standard air dives: 1950 - 1970. NMRI Technical Report No. 85-16, Naval Medical Research Institute, Bethesda, Maryland, 1985.

18. Weathersby, P.K., Survanshi, S.S., Nishi, R.Y., Thalmann, E.D., Statistically Based decompression tables VII. Primary data for testing human N_2O_2 decompression models. NSMRL Report No. 1182 and NMRI Technical Report No. 92-85, Naval Submarine Medical Research Laboratory, Groton, CT, 1992.

19. Weathersby, P.K., Survanshi, S.S., Homer, L.D., Parker, E.C. and Thalmann, E.D., "Predicting the time of occurrence of decompression sickness," Journal of Applied Physiology, Vol. 72, No. 4, pp.1541-1548, 1992.

20. Weathersby, P.K., Survanshi, S.S., and Nishi, R.Y. "Relative decompression risk of dry and wet chamber air dives." Undersea Biomedical Research, Vol. 17, No. 4, 1990.

21. Weathersby, P.K., Hart, B.L., Flynn, E.T., and Walker, W.F. "Role of oxygen in the production of human decompression sickness." Journal of Applied Physiology, Vol. 63, No. 6, pp. 2380-2387, 1987.